REMARKS:

Claims 1-36 were presented in the original application. Claims 1-9, 23-25 and 32-36 have been withdrawn without prejudice to Applicants' rights to pursue these Claims in other patent applications.

Applicants discussed amendments to the claims with Examiner Brandon Fetterolf, Ph.D., in a telephone interview on July 18, 2006 attended by Dr. Charles Romano, Mr. Kevin Kercher, and Dr. Elbert Chiang to address the rejections over alleged lack of enablement of the compound for imaging or controlling tumors . Since the claims at issue are directed to compositions and methods of preparing the compositions, it was indicated that this issue could be simply addressed by deleting superfluous claim language directed to uses of the compositions.

In a subsequent personal interview with Examiner Brandon Fetterolf on August 24, 2006 by Dr. Charles Romano, the outstanding obviousness rejections over Gubler et al., Slaninova et al., Dean et al., and Black et al. were discussed. The uncertainty associated with combining chelating groups with receptor binding peptides to obtain receptor-binding competent peptide derivatives was discussed in light of Reubi et al., Eur. J. Nucl. Med. 25(5):485. The absence of sequence similarity between the peptide sequences taught by Black et al. and the claimed peptide sequences was also discussed.

RESTRICTION

In the Examiner's Response to Election/Restriction Requirement, the previous Examiner affirmed the Applicant's traversal of the original Restriction Requirement of October 7, 2005, conceding that SEQ ID NO:13, 14, and 19-23 represent species that fall under the generic SEQ

ID NO:27 of Claim 12. Examiner therefore re-restricted the previously elected Group VII (Claims 12-14, 25, 27-31) to seven (7) different sub-generic inventions as follows:

1. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO:19, classified in class 514, subclass 2.

2. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 20, classified in class 514, subclass 2.

3. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 21, classified in class 514, subclass 2.

4. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 22, classified in class 514, subclass 2.

5. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO:23, classified in class 514, subclass 2.

6. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 13, classified in class 514, subclass 2.

7. Claims 13, 27-29, 31 drawn to pharmaceutical composition, a labelled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 14, classified in class 514, subclass 2.

Applicants elected Group 3 (i.e., Claims 13, 27-29, 31) as the sub-generic group for examination in the telephone interview on March 14, 2006. Applicants hereby affirm in writing their election of Group 3, which is drawn to SEQ ID NO:21 as a representative specie, for examination. Applicants identify Claims 12-14, 27-31 as the claims corresponding to this election (i.e., claims drawn to the generic SEQ ID NO:27 and specie SEQ ID NO:21).

Within Group 3, Applicants elected the following species: ^{111}In as the representative radioactive metal isotope, Gd as the representative paramagnetic metal, ^{125}I as the representative radioactive halogen isotope, and DOTA as the representative chelating group.

SPECIFICATION

Applicants have amended the abstract of the disclosure in accordance with MPEP §608.01 (b), as directed by the previous Examiner.

Applicants have amended The Brief Description of the Drawings according to the previous Examiner's recommendations. Paragraphs 109, 113, 117, and 120 of "The Brief

Description of the Drawings" no longer describes displacement curves for Compounds 13-15 in Figures 1-4. Paragraphs 110 and 120 of The Brief Description of the Drawings" also now identifies SS-14 as somatostatin in the figure legends of Figures 1 and 4. By convention in the field of receptor biology, SS-14 refers to the 14 amino acid peptide corresponding to a proteolytically processed form of somatostatin. Applicants state that no new matter has been added to the specification.

CLAIM OBJECTIONS

Applicants have amended the general formula "H -$(Xaa)_n$ -$(Xbb)_m$ -Tyr –Xcc-Gly -Trp - Xdd -Asp -Phe -R_2(I)" in Claims 12 and 31 to recite "H -$(Xaa)_n$ -$(Xbb)_m$ -Tyr –Xcc-Gly -Trp - Xdd- Asp -Phe -R_2."

Applicants have amended Claim 14 to depend properly from Claim 13 in conformance with 37 C.F.R. §1.75(c). More specifically, Claim 14 now further limits the subject matter of Claim 13 by specifying ^{111}In as the chelated metal isotope (i.e., "and wherein said metal isotope is ^{111}In.)

Applicants have cancelled duplicate Claim 30 to comply with the requirements under 37 C.F.R. §1.75(c).

CLAIM REJECTIONS

Claim Rejection under 35 U.S.C. § 112, Second Paragraph

The previous Examiner rejected the pending claims for insufficient antecedent basis under the second paragraph of 35 U.S.C. § 112. The previous Examiner specifically objected to

the use of the term "[t]he labelled peptide of Claim 12" used in then pending Claims 27-30 for lack of antecedent basis in Claim 12. Applicants have amended currently pending Claims 28-29 to recite "the composition of Claim 12". As Claim 12 is clearly drawn to a composition, Claims 28-29 as currently amended thus find sufficient antecedent basis for this preamble phrase.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

1. Claims 12-14, 27-30 were rejected under 35 U.S.C. §112, first paragraph as failing to provide enablement commensurate with the scope of the claimed invention. Specifically the claims drawn to a pharmaceutical composition are rejected for a lack of enabling support in the specification, which is alleged only to disclose a "labelled peptide" (Page 9, first sentence of the last paragraph of the April 11, 2006 Office Action). In paragraph [0065] on page 10, the specification provides clear support for the pharmaceutical composition of the claims:

> "a pharmaceutical composition, ... comprising in addition to a pharmaceutically acceptable carrier material ... and, if desired at least one pharmaceutically acceptable adjuvant, ... as the active substance a peptide derived from a compound of the general formula ..."

Moreover, support in the specification exists for the individual components (i.e., the labelled peptide, a pharmaceutically acceptable carrier, and a pharmaceutically acceptable adjuvant) of the pharmaceutical composition. The disclosure of the labelled peptide in the specification, which the previous Examiner has duly acknowledged, is relevant because the labelled peptide is the active substance of the pharmaceutical composition (page 11, paragraphs [0068] and [0069] taken together). Additionally, the specification and claims both recite that the pharmaceutical

composition may comprise a pharmaceutically acceptable carrier, as well as at least one pharmaceutically acceptable adjuvant. The specification specifically favors "a physiological saline" as a class of pharmaceutically acceptable carriers (page 10 in paragraph [0065]) and specifically recites "buffering agents such as HEPES buffer, TRIS buffer, etc., antioxidants and stabilizers such as ascorbic acid, gentisic acid or salts of these acids" as being pharmaceutically acceptable adjuvants (page 11 in paragraph [0068]). Thus the specification contains support for the claimed pharmaceutical compositions.

Responsive to the previous Examiner's allegation that the claims to a pharmaceutical composition are insufficiently enabled for an inherent "*in vivo* use thereof for treatment," Applicants first note that the currently pending claims are drawn to a composition and not to a method of treatment. Furthermore, Applicants have now amended the currently pending claims directed to the composition (Claims 12-14, 28, 29) such that they are not limited by a recited use. As MPEP § 2164.01(c) states:

> "[In contrast,] when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use."

The previous Examiner's arguments alleging lack of i*n vivo* efficacy of the claimed invention as a diagnostic or therapeutic agent are thus irrelevant to the currently pending composition claims. Furthermore, case law has repeatedly held that Applicants need not demonstrate *in vivo* or other efficacy to meet the either the utility requirements of 35 U.S.C. §101 or the enablement requirement of 35 U.S.C. §112 (*In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *In*

re Jolles, 628 F.2d 1322, 1326 n.10, 206 USPQ 885, 889 n.11 (CCPA 1980); also see MPEP § 2107).

To meet the utility requirements of 35 U.S.C. §101 or the enablement requirement of 35 U.S.C. §112, the courts have consistently held that the Applicant simply need only demonstrate a reasonable correlation between the activity in question and the asserted utility (*Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980); also see MPEP §2107). In this regard, Applicants have clearly demonstrated the specific binding of the derivatized peptide to CCK-B receptors in tumor tissue. The specific binding of the labelled derivatized CCK-peptides to the CCK-B-receptor is shown in Examples 4-7 of the specification. Importantly, the instant invention was enabled in isolated tumor tissue, and not in cell culture as indicated by the previous Examiner. Specific binding of the labelled peptides to isolated tumor tissues, as demonstrated by the Applicants in the specification, is recognized by those skilled in the art as being an important indicator of potential *in vivo* activity. In this instance, the labelled peptides and methods disclosed and fully enabled by this instant application have been used to image CCK-B receptor expressing tumors in human patients (Kwekkeboom et al., Eur. J. Nucl. Med.27(9):1312, 2000, provided in the March 25, 2004 Information Disclosure Statement). It is thus clear that the application as filed clearly meets the requirements for utility and enablement as per the established case law cited above.

2. Claims 12-13, 27-28 were rejected under 35 U.S.C. §112, first paragraph as failing to provide enablement of the claims directed to SEQ ID NO:27. More specifically, the Examiner

alleged that the specification fails to provide working examples or objective evidence that any of the species encompassed by the generic SEQ ID NO:27 can be used to successfully treat tumors (Page 14 of the April 11, 2006 Office Action). The Examiner further alleged that the Applicants had not enabled peptides containing the modifications encompassed by SEQ ID NO:27 and that the Applicants merely suggested random experimentation to identify such variants. As previously discussed, the Examiner's arguments with respect to enablement of tumor treatment have been rendered moot by the amendments to the currently pending composition claims that are not limited by a recited use. Furthermore, the application as originally filed does provide working examples and objective evidence for the operability of the invention as claimed.

Regarding enablement of specific peptide modifications and derivations encompassed by SEQ ID NO:27, Applicants have in fact provided *in vitro* working examples of the derivatized peptides (Compounds 16-26) binding to CCK-receptors. In Figure 2, Compounds 19-24 are enabled for the use of amino acid substitutions at positions Xbb, Xcc, and Xdd and for the addition of a chelator. Enablement is shown by the ability of the peptides corresponding to Compounds 19-24 to retain affinity for the CCK-B-receptor after modifications have been made to SEQ ID NO:27. Compounds 19-24 encompass three different amino acid substitutions in position Xbb (i.e., Asp, D–Asp, and Dpr), three different amino acid substitutions in position Xcc (i.e., Met, Nle, and Thr) and two different amino acid substitutions in position Xdd (i.e., Met and Nle). In addition, two means of attaching the chelator to the N-terminal peptide are described (i.e., α-configuration, β-configuration). Lastly, Figure 3 shows enablement of the derivatized peptides chelated with ^{115}In.

Responding generally to the previous Examiner's comments on the importance of amino acid substitutions, Applicants agree that *a priori* any given amino acid residue may be structurally and functionally important or not. As the previous Examiner states:

> "Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited."

However, predictions made based on the degree of sequence conservation coupled with direct testing can enable changes to be made in certain positions of certain peptides with a reasonable expectation of maintaining function.

One possible line of evidence that speaks of the importance of a particular amino acid residue is sequence conservation, as a reflection of the strong selection for the functional or structural importance of that residue. In two examples provided by the previous Examiner (Burgess et al., 1990; and Wen et al., 2001), the amino acid substitutions made by the authors were in residues taught by references therein to be conserved. Therefore there was a reasonable expectation that function would be lost by targeting those conserved residues, consistent with the authors' hypothesis. Wen et al. and references therein teach that a mutation in the conserved catalytic domain of the phosphatase PTEN can inactivate PTEN. Burgess et al. provide similar validation for such hypotheses concerning conserved residues on page 2135, column 2, line 2:

> "It was suggested that modification of this residue, which is conserved in all HGF-1 and HGBF-2 sequences reported to date, was responsible for [the observed effects]. The results presented here using site-directed mutagenesis to address the role of lysine 132 on the functional properties of HGBF-1 are in general agreement with the conclusions of Harper and Lobb (19)." [emphasis added]

Although the field of protein chemistry can be unpredictable at times, teachings in the prior art such as those cited herein by the Examiner on the conservation of a residue can indicate its structural or functional importance.

A more direct line of evidence that speaks of the importance of a particular amino acid residue is the empirical determination by testing actual substitutions. Applicants note in many ways empirical observation is stronger than arguments based on mere conservation. Lazar et al., 1998, cited by the Examiner, is a good example of the need for direct replacement especially in cases where conservation may not correlate as strongly with a residue's importance. As presented in the abstract on page 1247, line 7:

> "When aspartic acid 47 was mutated to alanine or asparagine, biological activity was retained; in contrast, substitutions of this residue with serine or glutamic acid generated mutants with reduced binding and colony-forming capacities."

Therefore directly testing specific substitutions provides the most accurate conclusion of permissible substitutions. Without attempting direct replacement of aspartic acid with several amino acids, Lazar et al. would not have detected the subtle effects of replacement by some of the substitutions.

As empirical observation relates to the instant invention, the residues deemed capable of substitution are taught through Applicants' own working examples and by other references known to those of skill in the art at the time of filing (see MPEP §2164.05(a)). As mentioned previously, Applicants' own examples show that various substitutions at positions Xbb, Xcc, and Xdd are permissible. In Figure 2, the ability of Compounds 19-24 to retain affinity for the CCK-B-receptor is shown after substitutions have been made to SEQ ID NO: 27 at positions Xbb (i.e., Asp, D–Asp, and Dpr), Xcc (i.e., Met, Nle, and Thr) and Xdd (i.e., Met and Nle). Furthermore,

at the time of filing those skilled in the art appreciated that substitutions could be made in the CCK-8 peptide at the positions corresponding to Xbb, Xcc, Xdd, without compromising peptide binding to its receptor (see Edmundson et al., 1985; Richards et al., 1990; and Moroder et al., 1981, provided in May 7, 2004 IDS; also see Hruby et al. (Int J Pept Protein Res. 1990 Jun;35(6):566-73 in IDS submitted with this Response). Consequently, the state of the prior art at the time of filing was such that those skilled in the art would appreciate that substitutions are permissible at the positions corresponding to Xbb, Xcc, Xdd of SEQ ID NO:27 without compromising function (i.e., binding). Therefore Applicants have thus carefully defined and enabled residues they believe to be capable of substitution or to be invariant in SEQ ID NO:27.

While obtaining useful analogs at the substituted positions may be desirable, Applicants are not suggesting random experimentation or screening, as implied by the previous Examiner. On the contrary, Applicants believe that any substitutions at the variable positions will function as claimed. Merely, the claims, as originally written, were meant to encompass derivatized peptides capable of binding CCK-B-receptors, including those with naturally occurring CCK-8 sequences as well as sequences for CCK-8 peptide analogs. In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court has stated:

> "[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification."

Therefore Applicants believe that they are entitled to the claim to the genus of compounds represented by SEQ ID NO:27 because they have enabled several species under the genus and because the state of the art at the date of filing enabled many of the indicated amino acid substitutions.

3. Claims 12-14, 27-28 were rejected under 35 U.S.C. §112, first paragraph as failing to provide enablement of the claims directed to SEQ ID NO:21. Regarding the previous Examiner's allegation that the instant invention requires the enablement of a method of treatment for all types of tumors, the Applicants once again note that the claims are directed to a compound and not a method of treatment and that enablement of a treatment (i.e., a method) is not necessary for a composition claim (see MPEP §2164.01).

Regarding enablement of the peptides corresponding to SEQ ID NO:21 for binding CCK-B receptors in tumor tissue, Applicants have provided *in vitro* working examples of the derivatized peptides (Compounds 16-26) as discussed in the response to the enablement of SEQ ID NO:27 above. Specific binding of SEQ ID NO:21 to CCK-B receptors in tumor tissue sections is shown in Figures 2A and 2B.

Rejection 1 under 35 U.S.C. §103

Claims 12, 27-28, 31 were rejected under 35 U.S.C. §103(a) over Gubler et al., in view of Slaninova et al., and in further view of Dean et al.

Gubler et al. do not teach, suggest, nor anticipate the invention as currently claimed, (i.e., a peptide of the general formula $\underline{H\text{-}(Xaa)_n\text{ - }(Xbb)_m\text{ - Tyr - Xcc — Gly - Trp - Xdd —Asp - Phe -}}$

wherein a chelating group is bound by an amide bond or through a spacing group to the N-terminal amino acid residue of said peptide). Gubler et al. does teach a naturally-occurring CCK-8 peptide. The naturally-occurring porcine CCK-8 peptide disclosed in Gubler et al. has the same sequence as the naturally-occurring CCK-8 peptides in human and rat, including the C-terminal modification by amidation. However, the amidated peptide of Gubler et al. differs significantly from the peptide of the claims as currently amended and Gubler et al. do not teach or suggest any of these dissimilar features. Gubler et al. mainly teach the cloning of the preprocholecystokinin gene in pig and utilization of nucleotides comprising the isolated sequence to characterize the expression of CCK in the porcine brain and gut. Gubler et al. do not teach the detection of CCK receptors by using CCK peptides, as described in the instant invention. However Gubler et al. do teach the detection of CCK expression in porcine brain and gut by use of cDNA probes to mRNA or by creation of oligonucleotide probes for primer extension. Gubler et al. did not characterize CCK-receptor expression and their study did not involve the use of CCK peptides. Furthermore, any motivation to exploit the binding of the naturally-occurring CCK-8 peptide to the CCK receptor is lacking from Gubler et al. As Gubler et al. themselves summarize potential avenues of research based on their discovery on page 4310, column 1-2:

> "Our CCK cDNA clones should be useful for a number of purposes. Expression studies using different cell types should further elucidate the posttranslational processing and modifications that play an important role in the physiology of CCK. Hybridization histochemistry should allow localization of sites of mRNA synthesis. Quantitations of mRNA levels in different brain and gut regions will complement the measurements of CCK peptide levels that have already been made. Finally the clones should allow the study of the genomic structure of porcine CCK as well as the isolation of human CCK mRNAs."

Therefore Gubler et al. do not teach, suggest, nor anticipate the invention as currently claimed.

Slaninova et al. do not teach, suggest nor anticipate the invention as currently claimed (i.e., a peptide of the general formula H-$(Xaa)_n$ - $(Xbb)_m$ - Tyr - Xcc — Gly - Trp - Xdd —Asp - Phe - wherein a chelating group is bound by an amide bond or through a spacing group to the N-terminal amino acid residue of said peptide). Slaninova et al. teach radiolabeling of a CCK-8 peptide analog by coupling ^{125}I to the tyrosine residue. Slaninova et al. do not teach nor suggest the use of a chelating group. Moreover Slaninova et al. do not teach the use of isotopes or atoms other than ^{125}I for labeling. Therefore Slaninova et al. do not anticipate the invention of the currently amended claims.

Dean et al. simply teach the use of the chelator to label proteins, specifically antibody fragments.

For any group of references to render an invention obvious, there must be a reasonable expectation of success that the references could be combined to arrive at the invention as claimed (see MPEP §2143.02). Moreover, because of the unpredictability of the technology, there is no reasonable expectation of success when combining chelators with receptor binding peptides. As MPEP §2144.08 (e) states:

> "If the technology is unpredictable, it is less likely that structurally similar species will render a claimed species obvious because it may not be reasonable to infer that they would share similar properties." See, e.g., *In re May*, 574 F.2d 1082, 1094, 197 USPQ 601, 611 (CCPA 1978); *In re Schechter*, 205 F.2d 185, 191, 98 USPQ 144, 150 (CCPA 1953)

Although a peptide of any length may be considered a protein by default, the effect of coupling a chelator to a protein, as in Dean et al., does not make any prediction that the effect of coupling a chelator to a peptide will result in success. References generally teach that addition of large DTPA or DOTA chelating groups with or without metal atoms can impact peptide receptor

binding (e.g., Reubi, Endocr. Rev. 2003 Aug;24(4):389-427; column 2, first full paragraph, page 392, provided in the IDS accompanying this Response). Due to the extreme difference in size between a short peptide and a protein, especially relative to the size of the chelator, those of skill in the art can imagine that attaching a chelator to a short peptide presents challenges not present when attaching a chelator to a protein. The positioning or the mere presence of the chelator may interfere with binding of the peptide to its cognate receptor or sterically constrain the peptide in ways undesirable for binding due to the large size of the chelator in relation to a short peptide. In contrast, attaching the chelator to a protein the size of an antibody or an antibody fragment would not pose such problems, as many sites would be available for attaching the chelator away from any critical site conferring desired activity.

Because of the unpredictability of the technology, the addition of the chelator to the CCK-8 analogs did not provide a reasonable expectation of success. More specifically, one of skill in the art would not be able to predict that addition of the chelator would not abolish the ability of the peptide to bind its receptor. As MPEP 2143.02 states:

> "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)

Reubi et al. (Eur. J. Nucl. Med. 1998 25 (5):485:481-490; previously submitted on March 25, 2004) show that binding of the CCK-8 analog is sensitive to the positioning of the chelator and that attaching the chelator anywhere on the CCK-8 analogs does not predictably result in success. Specifically, the addition of DTPA to the C-terminus of CCK-8 analogs dramatically decreases binding affinity (Table 1. Compare MP2247 (IC50=2.3nM for CCKB-R) vs. MP2336

(IC50>100nM for CCKB-R). Consequently, the use of the chelator with a receptor binding peptide such as a CCK-8 derivative would not have been predictable. Moreover, there is nothing in any of the cited references indicating that addition of a chelating group to a CCK-8 peptide would be successful. Neither Gubler et al. nor Slaninova et al. teach CCK-8 peptides with chelating groups that can bind a CCK-receptor while Dean et al. only teach the attachment of a chelator to an antibody fragment (i.e., antimyosin Fab'). In the case of the invention as presently claimed, this combination of references provides no reasonable expectation that addition of a chelator would not undesirably alter or abolish the ability of the CCK-8 peptide analog to bind CCK receptors. Example 5 of the specification even states that "displacement curves of DTPA-substituted CCK-analogs ... are measured in order to determine the effect of the DTPA group", indicating the uncertainty of making this particular modification. In view of the unpredictability of the effects of chelator addition, the invention as currently claimed (i.e., a peptide of the general formula H-$(Xaa)_n$ - $(Xbb)_m$ - Tyr - Xcc — Gly - Trp - Xdd —Asp - Phe - wherein a chelating group is bound by an amide bond or through a spacing group to the N-terminal amino acid residue of said peptide) would not have been obvious in view of Gubler et al., Slaninova et al., and Dean et al.

Based on analysis of the references cited by the previous Examiner, the compound as presently claimed is structurally distinct from the compounds taught by the cited references. As evidenced by studies of the compounds of the claims as currently amended, retaining the receptor binding affinity of a peptide after attaching a large chelating group is an unpredictable art. Therefore the references cited do not present a case of *prima facie* obviousness of the compound of the instant invention as currently claimed.

Rejection 2 under 35 U.S.C. §103

Claims 12, 27-28, 31 were rejected under 35 U.S.C. §103(a) over Gubler et al., in view of Slaninova et al., and in further view of Dean et al. and in further view of Black et al.

As set forth above, Gubler et al., in view of Slaninova et al., and in further view of Dean et al., do not render the instant invention obvious. In further view of Black et al., the invention is also not obvious as there would be no motivation to combine Black et al. with the other references (see MPEP § 2143.01). Specifically, neither the nature of the problem to be solved, nor the teachings of the prior art, and nor knowledge of persons of ordinary skill in the art provide motivation to combine the teachings of Black et al. with those of any of the other references cited to arrive at the claimed invention. First of all, Black et al. is directed to an Interleukin 1β recognizing protease, inhibitors of that protease, and substrates of that protease. Those skilled in the art of identifying the radiolabeled peptides of this invention would not be motivated to seek guidance in this unrelated area. Furthermore, Black et al. teach the sequence R_1–Asp–R_2–R_3 where R_1 is any D or L amino acid, and R_2 is Ala or Gly. The sequences claimed (SEQ ID NO:21, SEQ ID NO:27) do not meet these limitations because Tyr rather than Ala or Gly is claimed in the corresponding R_2 position. It is not clear that anyone of skill in the art would be motivated to combine teachings directed to such dissimilar sequences.

Lastly, Black et al. teach that the sequence His-(DAsp)-Ala-Pro is poorly cleaved by the IL1β Protease (column 25 lines 30-36 and Table 1). As Table 1 clearly shows, replacing the L–Asp residue of peptide 1 with D–Asp (i.e., peptide 4) results in a reactivity of <0.01 for peptide 4 relative to peptide 1. Thus changing the L–Asp of the peptide to D–Asp would not be consistent

with the teaching of Dean et al. for preventing peptide accumulation as it would be predicted to decrease peptide proteolysis and thus increase peptide accumulation.

Therefore for the reasons cited, those skilled in the art would not be motivated to combine the teachings of Black et al. with Gubler et al., Slaninova et al., and Dean et al. to arrive at the invention as claimed.

CONCLUSION

It is not believed that extensions of time are required beyond those which may otherwise be provided for in documents accompanying this Response. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned for under 37 C.F.R. §1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account 20-0823.

Respectfully submitted,

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